NDA 14-214/S-050, S-051
NDA 17-430/S-026, S-027

NOV 23 1999

Sanofi-Synthelabo Inc.
Attention: Gary M. Lewis
Manager, Drug Regulatory Affairs
90 Park Avenue
New York, NY 10016

Dear Mr. Lewis:

Please refer to your supplemental new drug applications dated December 4, 1998 and April 27, 1999, received December 7, 1998 and April 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NegGram® (nalidixic acid caplets) Caplets, 250 mg, 500 mg, 1 g (NDA 14-214/S-050 and S-051 respectively).

Please refer to your supplemental new drug applications dated December 4, 1998 and April 27, 1999, received December 7, 1998 and April 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NegGram® (nalidixic acid suspension) Suspension, 250 mg/5 mL (NDA 17-430/S-026 and S-027 respectively).

We acknowledge receipt of your submissions to both NDA 14-2 14 and NDA 17-430 dated May 21, 1999 and October 26, 1999, received May 24, 1999 and November 1, 1999.

These supplemental new drug applications provide for the following changes to the label:

1. PRECAUTIONS

- In the **Information for Patients** subsection, another paragraph was added as follows:

> "Patients should be advised that convulsions have been reported in patients taking quinolones, including Nalidixic acid, and to notify their physician before taking this drug if there is a history of this condition. Patients should be advised that mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, magnesium-based antacids, sucralfate or Videx®, (Didanosine), chewable/buffered tablets of the pediatric power for oral solution should not be taken within the two-hour period before or within the two--hour period after taking nalidixic acid (see **Drug Interactions).**"

- In the **Drug Interactions** subsection, the "antacids" statement was revised to read:

"Antacids containing magnesium, aluminum, or calcium; sucralfate or divalent or trivalent cations such as iron; multivitamins containing zinc; and Videx®, (Didanosine), chewable/buffered tablets or the pediatric power for oral solution may substantially interfere with the absorption of quinolones, resulting in systemic levels considerably lower than desired. These agents should not be taken within the two hour period before or within the two-hour period after nalidixic acid administration."

- **A Geriatric Use** subsection was added as follows:

"Clinical studies of NegGram® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using nalidixic acid in elderly patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, General.)"

2. DOSAGE AND ADMINISTRATION

- An antacid statement was added to this section as follows:

"Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as. iron; multivitamins containing zinc; or Videx® (didanosine), chewable/buffered tablets of the pediatric powder for oral solution should not be taken within the two-hour period before or within the two-hour period after taking nalidixic acid."

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 26, 1999). Please note that the company logo was omitted from the package insert submitted October 26, 1999. The logo should be included in the FPL.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 14-214/S-050, S-05 1 and NDA 17-430/8-026, S-027." Approval of these submissions by FDA is not required before the labeling is used.

NDA 14-214/S-050, S-051
NDA 17-430/S-026, S-027

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MID 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Robin Anderson, Regulatory Review Officer, at (301) 827-2127.

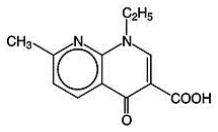
Sincerely,

Mark J. Goldberger, M.D M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

NegGram®
NALIDIXIC ACID, USP

DESCRIPTION

NegGram®, brand of nalidixic acid, is a quinolone antibacterial agent for oral administration. Nalidixic acid is 1-ethyl-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid. It a pale yellow, crystalline substance and a very weak organic acid.
Nalidixic acid has the following structural formula:



Inactive Ingredients-- SUSPENSION: Carbomer 934P, FD&C Red #40, Flavor, Parabens, Purified Water, Saccharin Sodium, Sodium Chloride, Sorbitol Solution. CAPLETS: Hydrogenated Vegetable Oil, Methylcellulose, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Yellow Ferric Oxide.

CLINICAL PHARMACOLOGY

Following oral administration, NegGram is rapidly absorbed from the gastrointestinal tract, partially metabolized in the liver, and rapidly excreted through the kidneys. Unchanged nalidixic acid appears in the urine along with an active metabolite, hydroxynalidixic acid, which has antibacterial activity similar to that of nalidixic acid. Other metabolites include glucuronic acid conjugates of nalidixic acid and hydroxy nalidixic acid, and the dicarboxylic acid derivative. The hydroxy metabolite represents 30 percent of the biologically active drug in the blood and 85 percent in the urine. Peak serum levels of active drug average approximately 20 mcg to 40 mcg per mL (90 percent protein bound), one to two hours after administration of a 1 g dose to a fasting normal individual, with a half-life of about 90 minutes. Peak urine levels of active drug average approximately 150 mcg to 200 mcg per mL, three to four hours after administration, with a half-life of about six hours. Approximately four percent of NegGram is excreted in the feces. Traces of nalidixic acid were found in blood and urine of an infant whose mother had received the drug during the last trimester of pregnancy. (See PRECAUTIONS **--** Drug Interactions **.**)

Microbiology

NegGram has marked antibacterial activity against gram-negative bacteria including *Enterobacter* species, *Escherichia coli, Morganella Morganii; Proteus Mirabilis, Proteus vulgaris,* and *Providencia rettgeri. Pseudomonas* species are generally resistant to the drug. NegGram is bactericidal and is effective over the entire urinary pH range. Conventional chromosomal resistance to NegGram taken in full dosage has been reported to emerge in approximately 2 to 14 percent of patients during treatment; however, bacterial resistance to NegGram has not been shown to be transferable via R factor.

Susceptibility Test

Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimates of antibacterial susceptibility. One such procedure recommended for use with a disc containing 30 mcg of nalidixic acid is the National Committee for Clinical Laboratory Standards (NCCLS) approved procedure. Only organisms from urinary tract infections should be tested. Results of laboratory tests using 30 mcg nalidixic acid discs should be interpreted using the following criteria:

Zone Diameter (mm)	Interpretation
$19	(S) Susceptible
14-18	(I) Intermediate
#13	(R) Resistant

Dilution Techniques: Broth and agar dilution methods, such as those recommended by the NCCLS, may be used to determine the minimum inhibitory concentration (MIC) of nalidixic acid. MIC test results should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
#16	(S) Susceptible
$32	(R) Resistant

For any susceptibility test, a report of "susceptible" indicates that the pathogen is likely to respond to nalidixic acid therapy. A report of "resistant" indicates that the pathogen is not likely to respond. A report of "intermediate" generally indicates that the test result is equivocal.
The Quality Control strains should have the following assigned daily ranges for nalidixic acid:

QC Strains
E. Coli
(ATCC 25922)

Disc Zone Diameter
22-28

MIC (mcg/mL)
1.0-4.0

INDICATIONS AND USAGE
NegGram is indicated for the treatment of urinary tract infections caused by susceptible gram-negative microorganisms, including the majority of *E. Coli, Enterobacter* species, *Klebsiella* species, and *Proteus* species. Disc susceptibility testing with the 30 mcg disc should be performed prior to administration of the drug, and during treatment if clinical response warrants.

CONTRAINDICATIONS
NegGram is contraindicated in patients with known hypersensitivity to nalidixic acid and in patients with a history of convulsive disorders.

WARNINGS
Central Nervous System (CNS) effects including convulsions, increased intracranial pressure, and toxic psychosis have been reported with nalidixic acid therapy. Convulsive seizures have been reported with other drugs in this class. Quinolones may also cause CNS stimulation which may lead to tremor, restlessness, lightheadedness, confusion, and hallucinations. Therefore, nalidixic acid should be used with caution in patients with known or suspected CNS disorders, such as, cerebral arteriosclerosis or epilepsy, or other factors which predispose seizures. (See ADVERSE REACTIONS **.**) If these reactions occur in patients receiving nalidixic acid, the drug should be discontinued and appropriate measures instituted.
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactoid reactions required immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.
Nalidixic acid and other members of the quinolone drug class have been shown to cause arthropathy in juvenile animals. (See PRECAUTIONS and ANIMAL PHARMACOLOGY **.**)
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including quinolones, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General

Blood counts and renal and liver function tests should be performed periodically if treatment is continued for more than two weeks. NegGram should be used with caution in patients with liver disease, epilepsy, or severe cerebral arteriosclerosis. (See WARNINGS **.**) While caution should be used in patients with severe renal failure, therapeutic concentrations of NegGram in the urine, without increased toxicity due to drug accumulation in the blood, have been observed in patients on full dosage with creatinine clearances as low as 2 mL/minute to 8 mL/minute.

Moderate to severe phototoxicity reactions have been observed in patients who are exposed to direct sunlight while receiving NegGram or other members of this drug class. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

If bacterial resistance to NegGram emerges during treatment, it usually does so within 48 hours, permitting rapid change to another antimicrobial. Therefore, if the clinical response is unsatisfactory or if relapse occurs, cultures and sensitivity tests should be repeated. Underdosage with NegGram during initial treatment (with less than 4 g per day for adults) may predispose to emergence of bacterial resistance. (See DOSAGE AND ADMINISTRATION **.**)

Information for Patients

Patients should be advised NegGram may be taken with or without meals. Patients should be advised to drink fluids liberally and not take antacids.

Patients should be advised that quinolones may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reactions.

Quinolones may cause dizziness and lightheadedness, therefore, patients should know how they react to NegGram before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that quinolones may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones. Patients should be advised to avoid excessive sunlight or artificial ultraviolet light while receiving nalidixic acid and to discontinue therapy if phototoxicity occurs.

Patients should be advised that convulsions have been reported in patients taking quinolones, including Nalidixic acid, and to notify their physician before taking this drug if there is a history of this condition.

Patients should be advised that mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, magnesium-based antacids, sucralfate or Videx®, (Didanosine), chewable/buffered tablets of the pediatric power for oral solution should not be taken within the two-hour period before or within the two--hour period after taking nalidixic acid (see DRUG INTERACTIONS)

Drug Interactions

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been reports of theophylline-related side effects in patients on concomitant therapy with quinolones and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted, as required.

Quinolones have been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and the prolongation of its plasma half-life.

Quinolones, including nalidixic acid, may enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation test should be closely monitored.

Nitrofurantoin interferes with the therapeutic action of nalidixic acid.

Antacids containing magnesium, aluminum, or calcium; sucralfate or divalent or trivalent cations such as iron; multivitamins containing zinc; and Videx®, (Didanosine), chewable/buffered tablets or the pediatric power for oral solution may substantially interfere with the absorption of quinolones, resulting in systemic levels considerably lower than desired. These agents should not be taken within the two hour period before or within the two-hour period after nalidixic acid administration.
Elevated serum levels of cyclosporine have been reported with the concomitant use of some quinolones and cyclosporine. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

Drug Laboratory Test Interactions
When Benedict's or Fehling's solution or Clinitest® Reagent Tablets are used to test the urine of patients taking NegGram, a false-positive reaction for glucose may be obtained, due to the liberation of glucuronic acid from the metabolites excreted. However, a colorimetric test for glucose based on an enzyme reaction (e.g., with Clinistix® Reagent Strips or Tes-Tape®) does not give a false-positive reaction to the liberated glucuronic acid.
Incorrect values may be obtained for urinary 17-keto and ketogenic steroids in patients receiving NegGram, because of an interaction between the drug and the *m* -dinitrobenzene used in the usual assay method. In such cases, the Porter-Silber test for 17-hydroxycorticoids may be used.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In lifetime studies in the rat given nalidixic acid in the diet, there was an increased incidence of preputial gland neoplasms in the treated males and clitoral gland neoplasms in the treated females. Studies in mice in which nalidixic acid was administered in the feed for two years, or was given in the feed for 76 weeks followed by no treatment for 9 weeks, gave equivocal evidence of carcinogenic activity.
Nalidixic acid was tested in the Ames bacterial mutagenicity test (maximum dose 33 mcg/plate) and the mouse lymphoma assay (L5178Y/TK; maximum dose 100 mcg/mL) with and without metabolic activation, and results were negative.

Pregnancy: Teratogenic Effects.
Pregnancy Category C.
NegGram has been shown to be teratogenic and embryocidal in rats when given in oral doses six times the human dose. NegGram also prolonged the duration of pregnancy especially at four times the clinical dose. There are no adequate and well-controlled studies in pregnant women. Since nalidixic acid, like other drugs in this class, causes arthropathy in immature animals, NegGram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS and ANIMAL PHARMACOLOGY **.**)

Nursing Mothers
It is not known whether NegGram is excreted in human milk. Because other drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NegGram, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in infants below the age of three months have not been established.

Usage in Patients Under 18 Years of Age
Toxicological studies have shown that nalidixic acid and related drugs can produce erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of most species tested. No such joint lesions have been reported in humans to date. Nevertheless, until the significance of this finding is clarified, this drug should only be used in patients under 18 years of age when the potential benefit justifies the potential risk. (See WARNINGS and ANIMAL PHARMACOLOGY **.**)

Geriatric Use
Clinical studies of NegGram® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has

not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using nalidixic acid in elderly patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, General.)

ADVERSE REACTIONS

Reactions reported after oral administration of NegGram include the following.

CNS effects: drowsiness, weakness, headache, and dizziness and vertigo. Reversible subjective visual disturbances without objective findings have occurred infrequently (generally with each dose during the first few days of treatment). These reactions include overbrightness of lights, change in color perception, difficulty in focusing, decrease in visual acuity, and double vision. They usually disappeared promptly when dosage was reduced or therapy was discontinued. Toxic psychosis or brief convulsions have been reported rarely, usually following excessive doses. In general, the convulsions have occurred in patients with predisposing factors such as epilepsy or cerebral arteriosclerosis. In infants and children receiving therapeutic doses of NegGram, increased intracranial pressure with bulging anterior fontanel, papilledema, and headache has occasionally been observed. A few cases of 6th cranial nerve palsy have been reported. Although the mechanisms of these reactions are unknown, the signs and symptoms usually disappeared rapidly with no sequelae when treatment was discontinued.

Gastrointestinal: abdominal pain, nausea, vomiting, and diarrhea.

Allergic: rash, pruritus, urticaria, angioedema, eosinophilia, arthralgia with joint stiffness and swelling, and anaphylactoid reaction. Erythema Multiforme and Stevens-Johnson syndrome have been reported with nalidixic acid and other drugs in this class. Rash was the most frequently reported adverse reaction. Photosensitivity reactions consisting of erythema and bullae on exposed skin surfaces usually resolve completely in 2 weeks to 2 months after NegGram is discontinued; however, bullae may continue to appear with successive exposures to sunlight or with mild skin trauma for up to 3 months after discontinuation of drug. (See PRECAUTIONS **.**)

Other: rarely, cholestasis, paresthesia, metabolic acidosis, thrombocytopenia, leukopenia, or hemolytic anemia, sometimes associated with glucose 6-phosphate dehydrogenase deficiency.

OVERDOSAGE

Manifestations: Toxic psychosis, convulsions, increased intracranial pressure, or metabolic acidosis may occur in patients taking more than the recommended dosage. Vomiting, nausea, and lethargy may also occur following overdosage.

Treatment: Reactions are short-lived (two or three hours) because the drug is rapidly excreted. If overdosage is noted early, gastric lavage is indicated. If absorption has occurred, increased fluid administration is advisable and supportive measures such as oxygen and means of artificial respiration should be available. Although anticonvulsant therapy has not been used in the few instances of overdosage reported, it may be indicated in a severe case.

DOSAGE AND ADMINISTRATION

Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as. iron; multivitamins containing zinc; or Videx® (didanosine), chewable/buffered tablets of the pediatric powder for oral solution should not be taken within the two-hour period before or within the two-hour period after taking nalidixic acid.

Adults. The recommended dosage for initial therapy in adults is 1 g administered four times daily for one or two weeks (total daily dose, 4 g). For prolonged therapy, the total daily dose may be reduced to 2 g after the initial treatment period. Underdosage during initial treatment may predispose to emergence of bacterial resistance.

Children. Until further experience is gained, NegGram should not be administered to infants younger than three months. Dosage in children 12 years of age and under should be calculated on the basis of body weight. The recommended total daily dosage for initial therapy is 25 mg/lb/day (55 mg/kg/day), administered in four equally divided doses. For prolonged therapy, the total daily dose may be reduced to 15 mg/lb/day (33 mg/kg/day). NegGram Suspension or NegGram Caplets of 250 mg may be used. One 250 mg tablet is equivalent to one teaspoon (5 mL) of the Suspension.

HOW SUPPLIED

Suspension (250 mg/5 mL tsp), raspberry flavored, bottles of
1 pint (NDC 0024-1318-06)
Caplets of 1 g, light buff-colored capsule-shaped tablets, bottles of
100 (NDC 0024-1323-04)
Caplets of 500 mg, light buff-colored capsule-shaped tablets, bottles of
56 (NDC 0024-1322-03)
500 (NDC 0024-1322-06)
Caplets of 250 mg, light buff-colored capsule-shaped tablets, bottles of
56 (NDC 0024-1321-03)
Store suspension at room temperature up to 25° C (77° F). Store 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F). [see USP Controlled Room Temperature]

ANIMAL PHARMACOLOGY

NegGram (nalidixic acid) and related drugs have been shown to cause arthropathy in juvenile animals of most species tested. (See WARNINGS **.**)

Long-term administration of nalidixic acid to rats resulted in retinal degeneration and cataracts. Hydroxynalidixic acid, the principal metabolite of NegGram, did not produce any oculotoxic effects at any dosage level in seven species of animals including three primate species. However, oral administration of this metabolite in high doses has been shown to have oculotoxic potential, namely in dogs and cats where it produced retinal degeneration upon prolonged administration leading, in some cases, to blindness.

In experiments with NegGram itself, little if any such activity could be elicited in either dogs or cats. Sensitivity to CNS side effects in these species limited the doses of NegGram that could be used; this factor, together with a low conversion rate to the hydroxy metabolite in these species, may explain the absence of these effects.